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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,148	11/09/2006	Malgorzata Konieczna	GRT/37-86	6122

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EXAMINER	
VU, JAKE MINH	

ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,148	KONIECZNA ET AL.	
	Examiner	Art Unit	
	JAKE M. VU	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 15-34* is/are pending in the application.

4a) Of the above claim(s) *15-17 and 30-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,18-29,33 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of Applicant's Amendment filed on 01/27/20110.

- Claims 21-34 have been added.
- Claims 21-34 have been added.
- Claims 1-11, 15-34 are pending in the instant application.
- Claims 15-17 and 30-32 are withdrawn from consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 21 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 21 recites the newly amended limitation of "a water content of at least 3%"; however, the specification as-filed only disclosed "3-6%" and does not provide a written description or set forth the metes and bounds of this phrase. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed and now change the scope of the instant disclosure as-filed. Such limitations recited in the

present claims, introduce new concepts and thus violate the written description requirement of the first paragraph of 35 U.S.C. §112.

Applicant is required to cancel the new matter in the response to this Office action. Alternatively, Applicant is invited to identify sufficient written support in the original specification for the "limitations" indicated above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11 and 18-29, 33-34 rejected under 35 U.S.C. 103(a) as being unpatentable over MITRA et al (US 5,955,105) as evidenced by HANDBOOK (Handbook of Pharmaceutical Excipients: 5th edition. pg. 134, 725 and 731-732 (2006)) and MSDS (Material Safety Data Sheet: L-Thyroxine, sodium salt) in view of EUROPEAN (European Pharmacopoeia (2002) pg. 1438) and FRANZ et al (US 2003/0032675) **are maintained** for reasons of record in the previous office action filed on 09/05/2008, 03/13/2009, 09/22/2009 and as discussed below.

Note, MITRA teaches having water content preferably at less than 4.5% (see col. 4, line 55-56), which reads on "at least 3%".

Response to Arguments

Applicant argues that claim 21 requires that the pharmaceutical formulation has a water content of at least 3% w/w. Instead of the definition used in claims 1 and 21, claim 20 defines 'pregelatinised starch' as containing about 5% free amylase, 15% free amylopectin, and 80% unmodified starch. None of these pharmaceutical formulations is disclosed by the cited documents (including MITRA). The Examiner finds this argument unpersuasive, because as discussed in the previous office action, the limitations of "wherein the pregelatinised starch is produced by subjecting moistened starch to mechanical pressure in order to rupture some or all of its starch granules and subsequent drying" and “pregelatinised starch contains about 5% free amylase, 15% free amylopectin, and 80% unmodified starch” are inherent to the pregelatinised starch (see European Pharmacopoeia at pg. 1438; Handbook of Pharmaceutical Excipients: 5th edition at pg. 731), wherein the secondary reference, FRANZ teaches using pregelatinized starch in levothyroxine compositions.

Applicant argues that Both HANDBOOK and EUROPEAN, which were cited by the Examiner, list the entities 'starch, pregelatinised' and 'starch' (unmodified) separately because they are universally recognized in the art as distinct excipients with very different properties and functionalities. It is not possible to merely substitute starch for pregelatinised starch in a pharmaceutical formulation without changing the characteristics of the formulation and, as such, they are not mere functional equivalents. The requirement of Applicants' claims to include pregelatinised starch provides the claimed formulations with different solubility characteristics as compared to other

formulations containing water-soluble, unmodified starch. Additionally, pregelatinised starch has a number of other different chemical and physical properties as compared to unmodified starch. Specifically, pregelatinised starch possesses enhanced flow and compression characteristics as compared to unmodified starch: pregelatinised starch granules occur as irregular chunks or thin plates, whereas unmodified starch occurs as a powder comprising very small spherical or ovoid granules. Thus, in contrast to the Examiner's assertion made to justify the obviousness rejection, 'pregelatinised starch' and 'starch' are clearly not functional equivalents. Furthermore, the compatibility with lubricants of pregelatinised starch and unmodified starch is different and altering the excipient may require a change in the choice of lubricant. Replacing the starch in the formulation of MITRA's Example 10, which has 0.5% magnesium stearate, with pregelatinised starch would be expected to have a not insubstantial effect on tablet strength and dissolution properties. Thus, the magnesium sterate lubricant may need to be replaced by stearic acid or the level of magnesium sterate reduced to compensate for that change (see HANDBOOK at page 731). Thus, pregelatinised starch is not merely an alternative for unmodified starch having some properties that may be used interchangeably since one of ordinary skill in the art making the Examiner's proposed substitution would have reasonably expected to make other changes in the formulation (e.g., choice and/or amount lubricant). The Examiner finds this argument unpersuasive, because starch and pregelatinised starch are not functional identical as argued by Applicant, but rather functional equivalents. Wherein starch and pregelatinised starch have equivalent functions of “tablet and capsule diluent, tablet and capsule disintegrant;

tablet binder" (see HANDBOOK at pg. 725, under Functional Category; and pg. 731 under Functional Category).

Applicant argues that formulations according to the present invention have the surprising (and totally unexpected) property that those with a higher moisture content (4.1 or 4.7%) display higher stability than those with a lower moisture content (2.4 or 2.7%). These results are shown in Table (C) at page 10 of Applicants' specification; the conclusions are summarized at page 7, lines 39-41, of Applicants' specification. For emphasis, new claim 21 requires that the pharmaceutical formulation have a water content of at least 3% w/w. This characteristic of Applicants' claimed invention is in clear contrast to MITRA's formulations, wherein the latter having a higher moisture content are found to be less stable than those having a lower moisture content. MITFW discloses that for some of the formulations, those with a moisture content of 4.5% are unstable whereas those with a moisture content of 3% are stable (column 4, lines 50-58). MITRA teaches away from the formulations claimed by Applicants because MITRA prefers a moisture content of 0-3%. Therefore, the problem facing one of ordinary skill in the art is that the formulations disclosed in MITRA must be produced in such a way as to minimize their moisture content in order for them to be stable. This would not have led to Applicants' claimed formulations. The Examiner finds this argument unpersuasive, because MITRA teaches having water content preferably at less than 4.5% (see col. 4, line 55-56), which reads on "at least 3%".

Applicant argues that the formulations of their claimed invention have a combination of microcrystalline cellulose and pregelatinised starch, which is partially

water soluble, in contrast to the water-soluble glucose polymer (i.e., unmodified starch) used in MITRA's formulations. The combination of microcrystalline cellulose and pregelatinised starch has been found to have the advantageous property of being stable at relatively high moisture content. This characteristic was neither suggested in the prior art of record nor would it have been obvious to one of ordinary skill in the art.

Applicants' invention provides a formulation that remains stable at relatively high water content. In contrast, MITRA teaches that lowering the moisture content is important to obtain a stable formulation, with a preference for a moisture limit of 0 to 3% (see column 4, lines 50-58). But drying a pharmaceutical formulation to obtain low levels of moisture is not straightforward and requires careful handling. This is especially true of a levothyroxine sodium-containing formulation due to the drug's thermal instability, which requires the use of low-temperature drying techniques in MITRA (see column 6, line 66, to column 7, line 5). Applicants' claimed formulations do not require the water content to be reduced to a low level (e.g., less than 3% wlw) to achieve stability. They are surprisingly stable even at higher levels as is demonstrated in Table (C) at page 10 of Applicants' specification. Therefore, it is established that the pregelatinised starch in the claimed invention unexpectedly provides a formulation that does not need to have the water level reduced to 3% w/w or less to achieve an acceptable stability, and that has an advantageous stability at higher moisture levels (e.g., at least up to 6% w/w). The Examiner finds this argument partially persuasive; however, as discussed above, because MITRA teaches having water content preferably at less than 4.5% (see col. 4, line 55-56), which reads on "at least 3%", wherein Applicant shows in Example 1(b) an

unexpected result for a water content of 4.7%, which is higher than MITRA, but Applicant's claims do not recite the formulation of Example 1(b). The Examiner assumes Example 1(b) could be claims 18, 19, 33 and 34, but was unable to correlate the amounts of ingredients with Example 1(b).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Telephonic Inquiries

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAKE M. VU whose telephone number is (571)272-8148. The examiner can normally be reached on Mon-Tue and Thu-Fri 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jake M. Vu/
Primary Examiner, Art Unit 1618